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Copper(I)-Catalyzed Asymmetric Pinacolboryl Addition of *N*-Boc-imines Using a Chiral Sulfoxide−Phosphine Ligand

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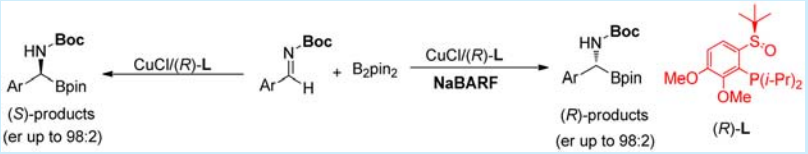
Supporting Information



ABSTRACT: Highly efficient and enantioselective copper(I)-catalyzed pinacolboryl addition of *N*-Boc-imines is reported. By using a single chiral sulfoxide-(dialkyl)phosphine (SOP) ligand, both enantiomeric isomers of α-amino boronic esters were obtained through an achiral counteranion switch.

Asymmetric transition-metal catalysis has emerged as one of the most effective synthetic methods for the preparation of enantiopure compounds.[1] One important target in this field is to identify the maximum of enantioinduction of a chiral metal catalyst (normally the complex of transition metal and chiral ligand) in a specific reaction. The ingenious nature of asymmetric catalysis, where high enantioselectivity requires only small differences in transition-state energies,[2] allows the use of more fragments than chiral ligands, e.g., counteranions, to affect the optical purity of products. Since most transition-metal catalysts are cationic, their nonbonding association with counteranions, particularly with the chiral nonracemic counteranions,[3] is able to direct stereochemical outcome and diversify asymmetric catalyzes. On the other hand, the use of achiral counteranions to promote cationic metal-catalyzed reactions has also received significant attention,[4] and many efforts have been made to increase enantioselectivity[5] or switch stereochemistry of reactions.[6]

Enantiopure α-amino boronic acids and esters,[7] owing to their substantial selectivity in the formation of reversible covalent bonds with the targeted enzyme, have emerged as a unique class of enzyme inhibitors[8] and been used as potential therapeutic agents.[9] In contrast to classic synthetic methods,[10] transition-metal-catalyzed addition of bis(pinacolato)diboron to imines can be the most efficient and straightforward approach to prepare α-amino boronate derivatives.[11] In 2008, Ellman[12a] pioneered a (ICy)Cu(I)-catalyzed borylation of chiral *N*-(*tert*-butanesulfinyl)aldimines and furnished a highly diastereoselective α-amino boronate ester.[12] Very recently, Morken reported an asymmetric platinum(0) phosphonite catalyzed strategy which converted aldehydes into applicable *N*-acyl-α-amino boronates.[13] As important as *N*-acyl-α-amino boronic acids are, their preparation through enantioselective borylative addition of *N*-acylimine still remains a challenge.[14] *N*-Boc-imine is a versatile and readily available starting material widely used in organic synthesis,[15] whereas the *N*-Boc-protected group can be easily removed for synthetic purposes. However, catalytic asymmetric pinacolboryl addition of *N*-Boc-imines, even in a nonasymmetric fashion, has not been reported. Since literature's strategy has been proved unsuitable for enantioselective diboration of *N*-acylimine,[13] a new and efficient catalytic approach is desirable to realize *N*-Boc-imine borylative addition. In this paper, we report a copper(I)-catalyzed pinacolboryl addition of *N*-Boc-imines, and high enantioselectivities were achieved by using a chiral sulfoxide phosphine ligand.

We recently demonstrated that chiral sulfoxide−phosphine ligands could promote CuCl-catalyzed highly enantioselective three-component borylative reaction.[16] In this study, a new class of chiral sulfoxide−(dialkyl)phosphine (SOP) ligands **L1**−**L5** were evaluated in CuCl-catalyzed enantioselective addition of $B_2(pin)_2$ to *N*-Boc-aldimine **1a** (Table 1, entries 1−5). (*R*)-Sulfoxide−(diisopropyl)phosphine **L4** provides *N*-Boc-α-amino boronic ester **3a**, with high enantiomeric ratio (8:92 er, Table 1, entry 4). As compared, commercially available (*S*,*S*)-Me-Duphos and (*R*)-BINAP gave rather low ers (<75:25) (see the Supporting Information). Various copper catalyst precursors, including CuBr and CuOAc, were tested in the reaction with ligand **L4**, and no good er values were observed (Table 1, entries 6 and 7). We further investigate a cationic copper(I) catalyst with the larger anion $BARF^-$ (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), which has been successfully applied in asymmetric catalysis.[17] This new [(*R*)-**L4**-Cu]$^+BARF^-$ catalyst, in situ generated by mixing CuCl, (*R*)-**L4**, and NaBARF in toluene, promoted the enantiomeric ratio of **3a** to 94:6 (Table 1, entry 8). It is interesting that the afforded α-amino boronic ester possesses a configuration opposite to that given by (*R*)-**L4**-CuCl catalyst.[18]

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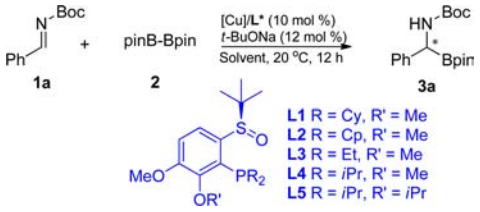
Table 1. Conditions Screening[a]



entry	[Cu]	L	solvent	yield[b] (%)	er[c]
1	CuCl	**L1**	Toluene	89	21:79
2	CuCl	**L2**	Toluene	93	22:78
3	CuCl	**L3**	Toluene	89	19:81
4	CuCl	**L4**	Toluene	90	8:92
5	CuCl	**L5**	Toluene	89	9:91
6	CuBr	**L4**	Toluene	65	12:88
7	CuOAc	**L4**	Toluene	85	11:89
8[d]	CuBARF	**L4**	Toluene	93	94:6
9[d]	CuBARF	**L4**	*t*-BuOMe	96	97:3
10[d]	CuBARF	**L4**	THF	85	30:70
11	CuCl	**L4**	THF	87	12:88
12[e]	CuCl	**L4**	*t*-BuOMe	89	6:94

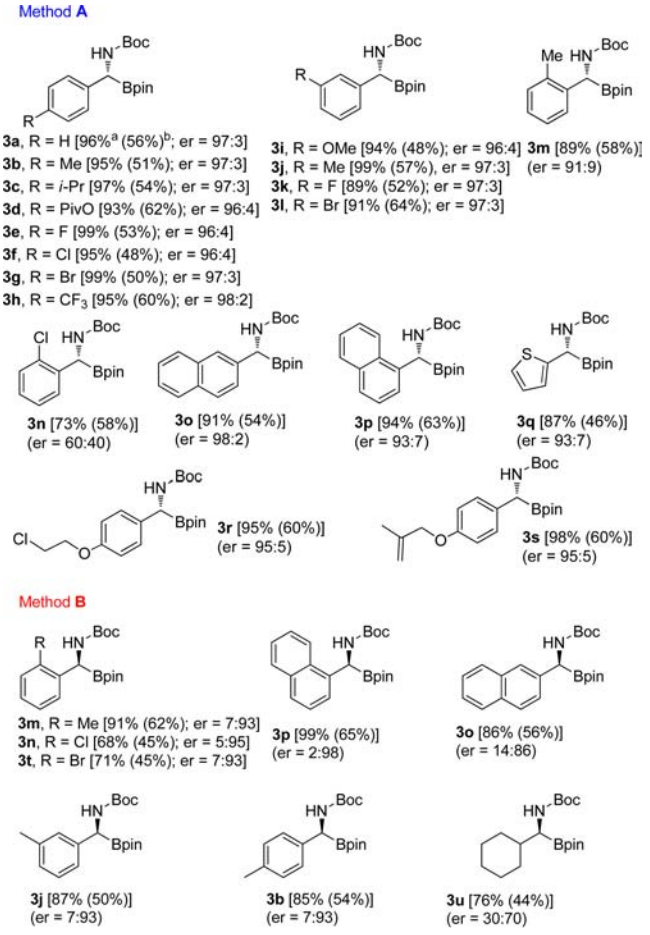
[a]Reaction conditions: 0.2 mmol of **1a**, 0.3 mmol of **2**, 10 mol % of metal salt (0.02 mmol), 12 mol % of **L** (0.024 mmol), 12 mol % of *t*-BuONa (0.024 mmol) in 1.5 mL of solvent, 20 °C, 12 h. [b]NMR yield and 2-methylnaphthalene as internal standard. [c]Enantiomeric ratio determined by chiral HPLC analysis. [d]12 mol % of NaBARF (0.024 mmol) as additive (method **A**). [e]*t*-BuOK (0.024 mmol) replaces *t*-BuONa (method **B**). BARF = (tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate).

In *t*-BuOMe, [(*R*)-**L4**-Cu]$^+$BARF$^-$ catalyst afforded **3a** with excellent yield (96%) and high er (97:3) (Table 1, entry 9) (method A), while (*R*)-**L4**−CuCl catalyst gave **3a** with 89% yield and 6:94 er (Table 1, entry 12) (method B). Notably, in THF, 1,4-dioxane, or DME, [(*R*)-**L4**−Cu]$^+$BARF$^-$ catalyst failed to switch the enantioface selectivity, probably due to these solvents coordinating to copper (Table 1, entry 10 vs entry 11).

With optimal reaction conditions in hand, the scope of substrates employing various *N*-Boc-aldimines was surveyed and is outlined in Scheme 1. By using [(*R*)-**L4**-Cu]$^+$BARF$^-$ catalyst (method A), the reaction is insensitive to the electronic effects of *para*- or *meta*-substituted aryl aldimines. Good to excellent yield (89−99%) and high er values (>96:4) were obtained with electron-rich or electron-poor substrates. Notably, the enantioselective borylative addition was tolerant of aryl aldimines containing a variety of functional groups such as acyloxy (**3d**), alkyl halide (**3h** and **3r**), and olefin (**3s**). Fused-ring (**3o** and **3p**) and hetero-ring (**3q**) aldimines also reacted well with high enantioselectivities. Although *ortho*-substituted aryl aldimines gave **3m** and **3n** in low er values. These limitations, fortunately, were complemented with (*R*)-**L4**−CuCl catalyst (method B) that effectively transformed *o*-Me-, *o*-Cl-, *o*-Br-substituted aryl aldimines and 1-naphthylaldimine to (*S*)-enantiomeric *α*-amino boronic esters in high optical purity (up to 98:2 er). For less bulky substrates, (*R*)-**L4**−CuCl catalyst can also provide (*S*)-**3** with moderate to good enantioselectivity. In addition, alkyl aldimine, **3u**, for instance, was also reactive, but low enantioselectivities were observed in both catalytic systems.

The absolute configuration of **3a** induced by [(*R*)-**L4**-Cu]$^+$BARF$^-$ catalyst was assigned to the (*R*)-configuration

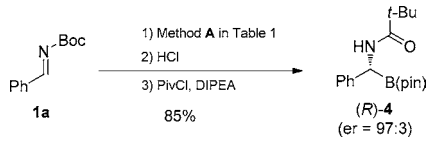
Scheme 1. Scope of Substrates



[a]NMR yield; [b]Isolated yield.

through a concise transformation of the crude product **3a** to the known (*R*)-**4**[13] in 97:3 er and 85% overall yield for three steps (Scheme 2). A plausible stereochemical model was proposed to

Scheme 2. Synthesis of (*R*)-4



rationalize this chiral induction. In the CuCl-catalyzed system, the initial catalytic precursor, [(*R*)-**L4**-CuCl]$_2$ complex characterized by X-ray crystallography, is first disassociated by *t*-BuOK to form (*R*)-**L4**-Cu^{t}Bu that then undergoes a *σ*-bond metathesis with $B_2(pin)_2$ and provides (*R*)-**L4**-Cu-Bpin species.[19] We reasoned that the formed borylcopper species adopts tetrahedron geometry on the copper atom and accommodates the Bpin moiety *trans* to the *tert*-butylsulfinyl group of the chiral sulfoxide−phosphine ligand (method B, Figure 1). Accordingly, *N*-Boc-benzaldimine coordinated to copper(I) complex as a *π* acid adopts the *cis*- to *tert*-butylsulfinyl group. Therefore, the Cu−B addition from the *Si*-face of the imine is favored because it avoids the steric hindrance between phenyl group and the *tert*-butylsulfinyl group. Conversely, in the CuBARF-catalyzed system, NaBARF disassociates the dimer to (*R*)-**L4**-Cu$^+$BARF$^-$, which allows the

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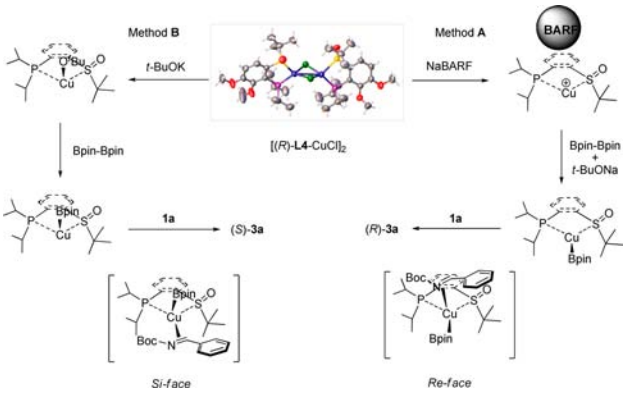
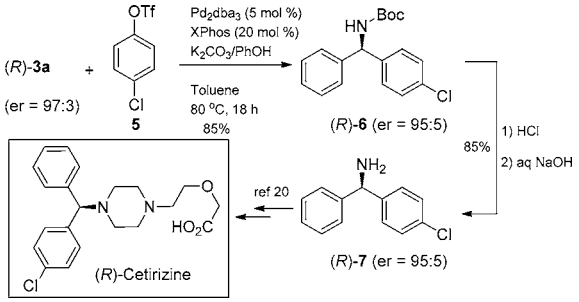


Figure 1. Plausible stereochemical models.

bulky counteranion ($BARF^-$) to locate *trans* to the *tert*-butylsulfinyl group of the chiral sulfoxide–phosphine ligand. Accordingly, the Bpin moiety approaches the cationic copper complex from the back side of the $BARF^-$ anion, and the formed borylcopper species gives rise to a facile coordination of imine *trans* to *tert*-butylsulfinyl group (method A, Figure 1). Thus, the migratory insertion of borylcopper to the imine bond is favorably *Re*-face selective and affords the (*R*)-product.

To demonstrate the utility of this strategy, we next studied the stereospecific cross-coupling of enantioenriched *N*-Boc-α-amino boronic esters and provided a new route to the synthesis of (*R*)-cetirizine (Zyrtec), an antihistamine agent (Scheme 3).[20]

Scheme 3. Formal Synthesis of (*R*)-Cetirizine



Ohmura and Suginome recently reported a highly stereospecific Suzuki–Miyaura reaction of enantioenriched α-(acylamino)-benzylboronic esters with aryl halides.[21] In our case, we found aryl trifluoromethanesulfonate (OTf) is a more effective partner to couple *N*-Boc-α-amino boronic esters. The stereoinvertive coupling of nonracemic (*R*)-**3a** (er = 97:3) and **4** was successfully accomplished to obtain (*R*)-**5** with high yield (85%) and good er (95:5). As expected, a concise and highly effective *N*-Boc deprotection of (*R*)-**5** under very mild condition completed the formal synthesis of (*R*)-cetirizine.

In conclusion, we present a highly enantioselective copper-(I)-catalyzed pinacolboryl addition of *N*-Boc-imines using a chiral sulfoxide–dialkylphosphine (SOP) ligand. Dramatic counteranion effect on stereochemical course was observed, and both enantiomeric isomers of α-amino boronic esters were obtained with high enantioselectivities. Further studies on the mechanism and utility of this strategy are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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